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U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

TRANSMITTAL FORM

(to be used for all correspondence after initial filing)

Total Number of Pages in This Submission

Application Number	10/828,316
Filing Date	April 21, 2004
First Named Inventor	Gertzman
Art Unit	1618
Examiner Name	Ebrahim
Attorney Docket Number	X-9468

ENCLOSURES *(Check all that apply)*

- [x] Fee Transmittal Form
- [x] Fee Attached
- [ ] Amendment/Reply
  - [ ] After Final
  - [ ] Affidavits/declaration(s)
- [ ] Extension of Time Request
- [ ] Express Abandonment Request
- [ ] Information Disclosure Statement
- [ ] Certified Copy of Priority Document(s)
- [ ] Reply to Missing Parts/ Incomplete Application
  - [ ] Reply to Missing Parts under 37 CFR 1.52 or 1.53
- [ ] Drawing(s)
- [ ] Licensing-related Papers
- [ ] Petition
- [ ] Petition to Convert to a Provisional Application
- [ ] Power of Attorney, Revocation Change of Correspondence Address
- [ ] Terminal Disclaimer
- [ ] Request for Refund
- [ ] CD, Number of CD(s) _____
  - [ ] Landscape Table on CD
- [ ] After Allowance Communication to TC
- [ ] Appeal Communication to Board of Appeals and Interferences
- [x] Appeal Communication to TC (Appeal Notice, Brief, Reply Brief)
- [ ] Proprietary Information
- [ ] Status Letter
- [x] Other Enclosure(s) (please Identify below):

Remarks

With Appendix

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT

Firm Name	GIPPLE & HALE		
Signature			
Printed name	John S. Hale		
Date	February 3, 2006	Reg. No.	25,209

CERTIFICATE OF TRANSMISSION/MAILING

I hereby certify that this correspondence is being facsimile transmitted to the USPTO or deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on the date shown below:

Signature			
Typed or printed name		Date	

PTO/SB/17 (01-06)
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U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Fees pursuant to the Consolidated Appropriations Act, 2005 (H.R. 4818).

FEE TRANSMITTAL For FY 2006

☐ Applicant claims small entity status. See 37 CFR 1.27

TOTAL AMOUNT OF PAYMENT ($) 500.00

Complete if Known	
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METHOD OF PAYMENT (check all that apply)

☑ Check ☐ Credit Card ☐ Money Order ☐ None ☐ Other (please identify): _____

☑ Deposit Account Deposit Account Number: 07-1340 Deposit Account Name: GIPPLE & HALE

For the above-identified deposit account, the Director is hereby authorized to: (check all that apply)

☐ Charge fee(s) indicated below ☐ Charge fee(s) indicated below, **except for the filing fee**

☑ Charge any additional fee(s) or underpayments of fee(s) under 37 CFR 1.16 and 1.17 ☑ Credit any overpayments

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FEE CALCULATION (All the fees below are due upon filing or may be subject to a surcharge.)

1. BASIC FILING, SEARCH, AND EXAMINATION FEES

	FILING FEES		SEARCH FEES		EXAMINATION FEES		
		Small Entity		Small Entity		Small Entity	
Application Type	Fee ($)	Fee ($)	Fee ($)	Fee ($)	Fee ($)	Fee ($)	Fees Paid ($)
Utility	300	150	500	250	200	100	
Design	200	100	100	50	130	65	
Plant	200	100	300	150	160	80	
Reissue	300	150	500	250	600	300	
Provisional	200	100	0	0	0	0	

2. EXCESS CLAIM FEES

Fee Description	Fee ($)	Small Entity Fee ($)
Each claim over 20 (including Reissues)	50	25
Each independent claim over 3 (including Reissues)	200	100
Multiple dependent claims	360	180

Total Claims		Extra Claims	Fee ($)	Fee Paid ($)
_____	- 20 or HP =	_____	x _____	= _____

HP = highest number of total claims paid for, if greater than 20.

Indep. Claims		Extra Claims	Fee ($)	Fee Paid ($)
_____	- 3 or HP =	_____	x _____	= _____

HP = highest number of independent claims paid for, if greater than 3.

Multiple Dependent Claims	
Fee ($)	Fee Paid ($)
_____	_____

3. APPLICATION SIZE FEE

If the specification and drawings exceed 100 sheets of paper (excluding electronically filed sequence or computer listings under 37 CFR 1.52(e)), the application size fee due is $250 ($125 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).

Total Sheets		Extra Sheets		Number of each additional 50 or fraction thereof	Fee ($)	Fee Paid ($)
_____	- 100 =	_____	/ 50 =	_____ (round up to a whole number) x	_____	= _____

4. OTHER FEE(S)

	Fees Paid ($)
Non-English Specification, $130 fee (no small entity discount)	
Other (e.g., late filing surcharge): Appeal Brief	500.00

SUBMITTED BY

Signature		Registration No. (Attorney/Agent) 25,209	Telephone (703) 448-1770
Name (Print/Type)	John S. Hale, Gipple & Hale		Date February 3, 2006

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

In re Patent Application of	:	
GERTZMAN et al.	:	
Serial No.: 10/828,316	:	Examiner Ebrahim
Filed: April 21, 2004	:	Group Art Unit 1618
For: COMPOSITION FOR FILLING BONE DEFECTS	:	

Commissioner of Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

APPEAL BRIEF

REAL PARTY IN INTEREST

The real party in interest is Musculoskeletal Transplant Foundation.

RELATED APPEALS AND INTERFERENCES

There are no other appeals, interferences or judicial proceedings known to appellant or its legal representatives which may be related to, directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

02/08/2006 [illegible]
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STATUS OF THE CLAIMS

Claims 2, 7, 8, 10 and 21-28 curremtly in the proceeding have been rejected as being unpatentable as obvious under 35 U.S.C. 103(a) over Boyce et al. U.S. Patent Number 6,294,187 when combined with Sander et al. U.S. Patent Number 5,356,629 and Breitbart et al. U.S. Patent Number 5,700,289. Claim 10 had been previously cancelled but was erroneously carried over in the rejection in the final Office Action. Claims 2, 7, 8, 21-28 are being appealed.

STATUS OF THE AMENDMENTS

The Examiner issued a final rejection on August 3, 2005 rejecting the claims currently in the case. An Amendment was filed December 5, 2005 after the final rejection amending claims 21, 23 and 27 and presenting arguments as to why the combined cited references were not valid prior art. This Amendment was treated by the Examiner as a request for reconsideration and was held to not place the application in condition for allowance.

SUMMARY OF CLAIMED SUBJECT MATTER

The subject matter of independent claim 21 is directed toward a sterile formable bone composition having demineralized osteoinductive and osteoconductive bone particles added to a viscous carrier at a concentration ranging from 5-50%(w/w), the carrier being a hydrogel taken from a group consisting of chitosan and sodium alginate (p.10, lns. 5-7) in a phosphate buffered aqueous solution (p. 10, lns. 25-26), the hydrogel ranging from about 5.0% to about 20.0% (p. 15, lns. 19-21) by weight of the aqueous carrier solution and having a molecular weight ranging from ten thousand to three hundred thousand Daltons (p. 10, lns. 3-4) with a stable viscosity at a temperature ranging from about 22° C to about 37°C (p. 8, lns. 1-2) the composition having a pH ranging from about 6.8

to about 7.4 (p. 10, lns. 22-24; p. 11, ln. 3) and a growth factor additive added to the composition, comprising one or more of a group consisting of transforming growth factor (TGF-beta), insulin growth factor (IGF-1); platlet derived growth factor (PDGF), vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF) (numbers 1-23), osteopontin, growth hormones such as somatotropin cellular attractants and attachment agents (pg. 13, lns. 9-13).

The subject matter of independent claim 23 is directed toward a sterile formable bone composition having demineralized osteoinductive and osteoconductive allograft bone particles in an aqueous carrier solution, the bone particles being added to a viscous carrier at a concentration ranging from 5-50%(w/w), the carrier being chitosan (p. 10, lns. 5-6) in a phosphate buffered aqueous solution, ranging from about 5.0% to about 20.0% (p. 15, lns. 19-23) by weight of the aqueous carrier solution and cellular material taken from a group consisting of living cells, cell elements such as red blood cells, white blood cells, platelets, blood plasma, pluripotential cells, osteoblasts, osteoclasts, and fibroblasts, epithelial cells, and endothelial cells (p. 13, lns 3-8) present at a concentration of 10^5 to 10^8 per cc of the carrier (p. 16, lns. 2-4), the chitosan having a molecular weight ranging from ten thousand to three hundred thousand Daltons (p. 10, lns 3,4) with a stable viscosity and having a pH ranging from about 6.8 to about 7.4 (p. 10, lns. 22-24; p. 11, ln. 3).

The subject matter of dependent claim 2 (depending from claim 21) is directed to bone particles ranging from 100 microns to 850 microns in size at a concentration ranging from 20% tp 35% by weight of the composition (p. 15, lns. 17-30); (p. 12, lns. 22 and 26)

The subject matter of dependent claim 25 (depending from claim 23) is directed toward fibroblast growth factor (FGF) (numbers 1-23) in the amount of 2-4 milligrams in 10 cc of carrier solution. (p.16, lns. 10-11)

The subject matter of dependent claim 26 (depending from claim 26) is the same as claim 2 above.

The subject matter of dependent claim 28 (depending from claim 23) is directed to demineralized and non-demineralized chips . (p. 9, lns. 8-11)

GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

Whether the invention as defined in Claims 2, 7, 8 and 21-28 are unpatentable as obvious under 35 USC 103(a) over the cited prior art references to Boyce et al. U.S. Patent Number 6,294,187 in view of the combination of Sander et al. 5,356,629 and Breitbart et al. U.S. Patent Number 5,700,289.

ARGUMENT

1. Applicant traverses the Examiner's rejection of Claims 2, 7, 8, and 21-28 as being unpatentable under 35 USC 103(a) over the cited prior art references to Boyce et al. U.S. Patent Number 6,294,187 in view of the combination of Sander et al. U.S. Patent Number 5,356,629 and Breitbart et al. U.S. Patent Number 5,700,289.

The claims should be grouped into two groups, Group I comprising claims 2, 7, 8 and 21 directed toward the hydrogel carrier taken from a carrier group consisting of chitosan and sodium alginate with a growth factor and Group II comprising claims 23-28 directed towards a hydrogel carrier chitosan with cellular material.

A. Applicant traverses the Examiner's rejection of Claims 2, 7, 8, and 21 as unpatentable under 35 USC 103(a) over the cited prior art references to Boyce et al. U.S. Patent Number 6,294,187 in view of the combination of Sander et al. U.S. Number 5,356,629

and Breitbart et al. U.S. Patent Number 5,700,289.

The present application is directed toward a formable (malleable) sterile bone putty which is applied to a bone defect site to promote new bone growth. The putty is molded into the desired shape to fit the bone defect.

The claims of this group are directed toward a formable putty type sterile implant composition having a chitosan or alginate carrier having specific molecular weight containing milled demineralized bone particles and a growth factor which can be formed by the surgeon in the operating room and placed into the bone defect site to promote bone growth at the defect site.

The Boyce '187 patent (noted as primary art) simply teaches a shaped hardened load bearing osteoimplant bone structure formed of compressed bone particles and not powdered demineralized bone particles mixed in a carrier of sodium alginate an/or chitosan forming a formable putty composition.

Compressive forces typically ranging from about 2,500 to 60,000 psi are applied to bone particles in a press-mold to produce a hard chalk-like material. (Col 11, lns 65-66) The material can then be easily shaped or machined into any of a wide variety of configurations. It should be specifically noted that in the preferred embodiment, the osteoimplant is provided with macro porosity, i.e. holes which enhance blood flow through the osteoimplant or the holes can be filled with a medically useful substance such as Grafton putty. As noted in the '187 patent the resulting osteoimplant can assume a determined or regular form or configuration such as a sheet, plate, disk, cone, pin, screw, tube, tooth, tooth root, bone or portion of bone, wedge or portion of wedge, cylinder, threaded cylinder (dowel) to name but a few. Of course, the osteoimplant can be machined or shaped by any suitable mechanical shaping means. In the preferred embodiment, the osteoimplant

possesses the configuration of a threaded cylinder (dowel) (Col 14, lns 6-16). It is also noted that the osteoimplant is applied at a bone repair site which requires mechanical support (Col 14, lns 21-25) and can be implanted using any suitable affixation means, c.g., sutures, staples, bioadhesives, and the like. (Col 14, lns 49-51)

The Boyce et al '187 compressed bone structure is formed by applying compressive force of at least about 1000 psi, has a bulk density greater than about 0.7 g/cm^3 and a wet composite strength substantially exceeding 3MPa to form a hardened mass. The bone particles which are used in the hardened structure are formed by milling whole bone to produce fibers, chipping whole bone, cutting whole bone, fracturing whole bone in liquid nitrogen or otherwise disintegrating the bone tissue. The bone particles range in average particle size from about 0.05 to about 1.2 cm in size and possess an average median length to median thickness of from about 1:1 to about 3:1. **Alternatively or in combination with the previously mentioned bone particles,** bone particles which are generally characterized as elongate and possessing relative high median length to median thickness ratios are utilized. The elongate particles are obtained by milling or shaving the surface of an entire bone with at least 60%, preferably 90% of the bone particles being elongated. These elongated particles possess a medium length from about 2 to 200 mm and preferably from about 10 to about 100mm. These elongate bone particles can possess a median length to median thickness ratio of at least about 50:1 up to about 500:1 or more. **In Boyce et al '187, preferably, at least about 60 weight percent, more preferably at least about 75 weight percent and most preferably at least about 90 weight percent of the bone particles utilized in the preparation of the bone particle-containing composition are elongate. It is noted that elongate bone particles provide an osteoimplant possessing particularly good compressive strength.** It can thus be seen that the characterization

of the Examiner that the sizes of the bone particles used in Boyce et al '187 correspond to that of the present invention is not correct. Furthermore there is no way that Boyce et al '187 could be characterized as formable. The composition fabricated in accordance with the Boyce et al '187 disclosure more preferably has a bone content ranging from about 50 to about 95 percent based on the weight of the entire composition.

As noted in the Examples of Boyce et al '187; the bone particles were mixed with different solutions such as glycerol (Examples 1, 12), cross linked with formalin (Examples 2 and 3), saline (Example 4), ethanol and ethyl cellulose (Examples 5, 6, 7, 8), and water (Examples 9, 10, 11). There is no teaching in the examples of the carrier of the present invention, the bone particle range, the weight of the carrier and range of the same, viscosity or any concentration of cellular material (Boyce et al '187 being a solid and having no viscosity). Applicant would point out that the use of hydrogels are disclosed only as a thickener when water and/or glycerol are used as the wetting agent for forming the slurry. These hydrogels are used to suspend and keep the bone particles separate during the application of the compression forces to form the solid structure and do not act as a carrier for the bone particles.

Chitosan is noted in Boyce et al '187 as a binder or an adhesive for the demineralized bone particles **and is incidentally found as one of a 60+ line list of suitable binders or adhesives.** (Col. 8, lns. 13-40) Preferred binders are polyhydroxybutyrate, polyhydroxyvalerate and tyrosine-based polycarbonates. When employed, binders will typically represent from about 5 to about 70 weight percent of the bone particle-containing composition calculated prior to compression of the composition.

Boyce et al '187 also envisions the use of fibers which will typically represent from about

5 to about 75 weight percent of the bone particle-containing composition.

Chitosan is also noted as a thickener to be used when the wetting agent is water and/or glycerol to preclude premature bone particle separation and improve suspension keeping characteristics of the composition (Col. 10, lns. 58-67 to Col. 11, lns. 1-10) prior to application of the compressive forces. This is used to keep the bone particles separate during application of the compressive forces to form the solid structure and not as a carrier for the bone products which is then directly applied to the wound site. Chitosan is not noted as being used in any of the Examples or in any of the preferred embodiments.

The Boyce et al '187 composition is heated in a mold during or after the compression step at a suitable temperature ranging from about 30° to about 70° C from 1 to 72 hours preferably 24 to 48 hours. Optionally it can be cross linked to improve the mechanical strength of the osteoimplant. Thus it is apparent that prior to final manufacturing steps of molding, heating and cutting the osteoimplant is not usable for application of a surgeon in the operating room.

The Boyce et al '187 reference cannot be combined with Sander '629 and/or Breitbart et al. '289 and does not teach or suggest the composition of the present invention in connection with the teachings of the Sander '629 patent and/or Breitbart et al. 289.

The Sander et al. '629 reference (noted as secondary art) **discloses the making of a bone cement to fill defects in bone.** The Examiner has argued that the '629 reference teaches: (1) a composition for bone repair comprising particles dispensed in a matrix; (2) that the composition can be implanted into defective bone tissue; (3) discloses the use of drugs and other substances that can induce bone growth; (4) that biocompatible particles of any size can be used in the composition and (5) that matrix material can be conveniently comminuted to appropriate particle size.

The bone cement of Sander et al '629 is formed by mixing biocompatible particles preferably polymethylmethacrylate coated with polyhydroxyethylmethacrylate (Examples 1 , 2 and 5 - 10) or particles of glycolide-lactide copolymer (Examples 3 and 4) in a matrix to obtain a molded semi-solid mass which can be suitably worked for implantation into bone. The biocompatible particles which are dispersed in the matrix can be formed from either bioabsorbable or nonbioabsorbable material. Suitable nonbioabsorbable material which can be used to form the biocompatible particles can be derived from xenograft bone, homologous bone, autogenous bone, hydroxyapatite and polymethylmethacrylate coated with polyhydroxyethylmethacrylate, the preferred nonbioabsorbable material. The weight of the nonbioabsorbable material in the wetted composition of Sander et al '629 runs from 35% to 75% (Dry weight 64% to 94%); to most preferably 45% to 60% (Dry weight 73% to 92%) with the more preferred weight being 40% to 70% (Dry weight 82% to 90%)(Col 4 lns 21 - 30). **There is no disclosure of demineralized bone used as the nonbioabsorbable material, in Sander et al '629 and demineralized bone is used as an additive in the nature of an osteogenic agent.** This bioactive substance is included as one or more medico-surgically useful substances such as a therapeutic agent, a growth promoting factor and osteogenic agent. It is noted in Col. 4 ln 40 to Col. 5 ln 17 that a bioactive substance can be introduced into the compositions, either directly into the matrix prior to or after wetting or into the biocompatible particles or polymethylmethacrylate particles, the preferred substance being polymethylmethacrylate. A growth promoting factor can be introduced into the composition such as fibroblast growth factor, bone growth factor, epidermal growth factor, platelet derived growth factor, macrophage derived growth factor, alveolar derived growth factor, monocyte derived growth factor, magainin and so forth. The bioactive substance can also be an osteogenic agent such as

osteoinductive protein, demineralized bone powder, in addition to morselized cancellous bone, aspirated bone marrow and other autogenous bone sources. As previously noted demineralized bone powder **is an additive of undetermined amount** and is included in a general laundry list and is not taught to be the biocompatible material, but rather an osteogenic agent.

In Examples 1 and 2 of the '629 patent, polymethylmethacrylate particles were coated with polyhydroxyethylmethacrylate carboxymethylcellulose or methylcellulose and water; Examples 3 and 4 use particles of glycolide-lactide copolymer; Examples 5 and 6 use particles of polymethylmethacrylate coated with polyhydroxyethylmethacrylate hydroxypropylmethylcellulose water; and Examples 7-10, use particles of polymethylmethacrylate coated with polyhydroxethylmethacrylate. The preferred nonbioabsorbable material was mixed with a matrix **HA (hyaluronic acid) having a molecular weight of about six hundred thousand Daltons**. Indeed **in all of the Examples no bone material of any type is used**. The use of demineralized bone in the range noted present invention results in an osteoinductive material which promotes bone growth.

Sander et al. '629 has a matrix (cellulose, ether, collagen, hyaluronic acid, pharmaceutically accepted salt of hyaluronic acid, derivative of hyaluronic acid and pharmaceutically acceptable salt of hyaluronic acid derivative and mixtures thereof) ranging from 6% to 36% by weight with 64% to 94% by weight of polymethylmethacrylate crystals. If one were to substitute demineralized bone material for the polymethylmethacrylate coated with polyhydroxyethacrylate of Sander et al '629, which substitution is not taught or suggested by this reference and is a completely different material, the range would be outside of the inventive range claimed.

Sander et al. '629 does not teach or obviate the present invention alone or combined with the

other cited references. Sander et al. '629 does not use or teach (1) demineralized bone material as the nonbioabsorbable material and as a major component of the composition; (2) an equivalent biocompatible material weight, (3) a carrier of chitosan or alginate; (4) a molecular weight of the carrier which is the same as the molecular weight of the inventive carrier; (5) a phosphate buffer to neutralize the composition, and (6) the addition of cellular material at a concentration of 10^5 to 10^8 per cc of the carrier. Furthermore Sander et al is not osteogenic relying on antigenic response.

The '629 reference does not suggest using demineralized bone together in a buffered isotonic salt carrier with a neutral osmolality or that such a combination is osteoinductive and medically beneficial in the repair of bone tissue. The Examiner's inference that the '629 patent teaches that the composition can comprise living cells such as erythrocytes, leucocytes and endothelial cells and that the pH of the composition is approximately 6.8-7.4 is not based on the teachings of the '629 patent and is a hind site supposition.

The Breithart et al '289 patent (noted as secondary art) is directed toward a sponge like matrix preferably constructed of a biodegradable, biocompatible synthetic polymer which uses the patient as the source of cells for the repair of bone defects. The cells are taken from the periosteum, (consisting of mainly multipotent mesodermal cells), isolated and seeded onto and into a matrix. In other embodiments, the matrix is formed of a material such as hydroxyapatite or mixtures of hydroxyapatite and polymer, or tricalcium phosphate. The matrix can also be sterilized bone or a porous metal alloy. The Examiner notes that Breithart et al '289 teaches (1) the use of alginate and chitosan. In regard to the disclosure of alginate and chitosan, in col. 6, lns. 20-40 a large laundry list (over 30 polymers) of potential natural and synthetic polymers are noted which can be used to form the fibrous matrix. Examples of natural polymers includes polysaccharides such as alginate. (Col.

6 ln 38) It is quite apparent that the matrix is solid as it is preferably made of hydroxyapatite, tricalcium phosphate, sterilized bone or metal alloy. In col. 10, lns. 7-10, the hydrogel which is noted is cross linked to form a three dimensional open-lattice structure includes alginate. In col. 10, lns. 43-45 alginate is disclosed as being used for hybridonia cell encapsulation, which has nothing to do with the present invention. In col. 11, lns. 27-40, chitosan is only noted for being a natural polycation such as the polysaccharide, chitosan. (Chitosan is not used as a carrier but as a cation) This is but one of a number of varieties of polycations which complex and stabilize the polymer hydrogel into a semipermeable surface membrane. Various examples are noted and it is offhandedly noted, that there exists natural polycations such as the polysaccharide chitosan.

The patent to Breitbart et al. '289 is directed toward periosteum cells seeded into a matrix (preferably a synthetic polymer) for repair of the bone defect. The '289 patent does disclose stem cells, chondrocytes and mesenchyma cells as follows: In Col. 2, lns. 45-60, it notes that prior art shows the use of autologous cells and chondrocytes attaching to hydroxyapatite. Col. 4, lns. 25-30 discloses the use of periosteum which consists of multipotent mesodermal cells. Col. 14, ln. 60 Claim 9 refers to periosteum cells seeded in biocompatible matrix.

Furthermore, none of the cited references disclose the additives of cells at a concentration of 10^5 - 10^8 per cc of carrier or a specific amount of growth factor added to 10cc of carrier.

In cases which are similar to the present circumstances, the courts have ruled that beyond looking at the prior art to determine if it suggests doing what the inventor has done, one must consider if the prior art provides an expectation of succeeding in the endeavor. *In re Dow Chem.*, 837 F.2d 469, 473, 5 U.S.P.Q.2d 1529, 1531 (Fed. Cir. 1988), "Both the suggestion and the expectation of success must be founded in the prior art, not in the applicant's disclosure." Id. As

stated by the court in the case of *In re Clinton,* "Obviousness does not require absolute predictability, but a reasonable expectation of success is necessary." *In re Clinton,* 527 F.2d 1226, 1228, 188 U.S.P.Q. 365, 367 (C.C.P.A.1976).

Furthermore as noted by the Court in the case of *In re Gordon,* the mere fact that a prior art reference could be modified to achieve the claimed invention does not make the modification obvious unless the prior art suggested the desirability of the modification. *In re Gordon,* 733 F.2d 900, 902, 221 U.S.P.Q. 1125, 1127 (Fed. Cir.1984); see also *In re Laskowski,* 871 F.2d 115, 117, 10 U.S.P.Q.2d 1397, 1398 (Fed. Cir. 1989), and *Ex parte Levengood,* 28 U.S.P.Q.2d 1300, 1302 (Bd. Pat. App. & Int. 1993). Applicants respectfully submit that nowhere in the art of record is there any suggestion to arrive at the claimed novel composition of the present invention.

The court in *Minnesota Mining & Manufacturing Co. v. Johnson &Johnson Orthopaedics, Inc.,* 24 USPQ2d 1321 (Fed. Cir 1992) held that: "Although [a patent's] specific claims are subsumed in [a prior art reference's] generalized disclosure..., this is not literal identity." The *Minnesota* court held that the reference's ranges were so broad as to be meaningless, and provided no guidance on how to construct a product with the patented invention's benefits.

The court in *In re Baird,* 29 USPQ2d 1550 (Fed. Cir. 1994), held that "The fact that a claimed compound may be encompassed by a disclosed generic formula does not by itself render that compound obvious." The *Baird* court further held that a disclosure to numerous compounds does not render obvious a claim to three compounds, particularly when that disclosure indicates a preference leading away from the claimed compounds.

As previously argued, none of the cited references singularly or in combination teach or obviate the present invention and indeed cannot be combined. The Examiner has engaged in

hindsight application, a prohibited rejection since *John Deere* to combine the cited prior art references against the present invention.

B. **Applicant traverses the Examiner's rejection of Claims 22-28 are unpatentable under 35 USC 103(a) over the cited prior art references to Boyce et al. U.S. Patent Number 6,294,187 in view of the combination of Sander et al. U.S. Patent Number 5,356,629 and Breitbart et al. U.S. Patent Number 5,700,289.**

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Compressive forces typically ranging from about 2,500 to 60,000 psi are applied to bone particles in a press-mold to produce a hard chalk-like material. (Col 11, lns 65-66) The material can then be easily shaped or machined into any of a wide variety of configurations. It should be specifically noted that in the preferred embodiment, the osteoimplant is provided with macro porosity, i.e. holes which enhance blood flow through the osteoimplant or the holes can be filled with a medically useful substance such as Grafton putty. As noted in the '187 patent the resulting osteoimplant can assume a determined or regular form or configuration such as a sheet, plate, disk, cone, pin, screw, tube, tooth, tooth root, bone or portion of bone, wedge or portion of wedge, cylinder, threaded cylinder (dowel) to name but a few. Of course, the osteoimplant can be machined

or shaped by any suitable mechanical shaping means. In the preferred embodiment, the osteoimplant possesses the configuration of a threaded cylinder (dowel) (Col 14, lns 6-16) . It is also noted that the osteoimplant is applied at a bone repair site which requires mechanical support (Col 14, lns 21-25) and can be implanted using any suitable affixation means, c.g., sutures, staples, bioadhesives, and the like. (Col 14, lns 49-51)

The Boyce et al '187compressed bone structure is formed by applying compressive force of at least about 1000 psi, has a bulk density greater than about 0.7 g/cm^3 and a wet composite strength substantially exceeding 3MPa to form a hardened mass. The bone particles which are used in the hardened structure are formed by milling whole bone to produce fibers, chipping whole bone, cutting whole bone, fracturing whole bone in liquid nitrogen or otherwise disintegrating the bone tissue. The bone particles range in average particle size from about 0.05 to about 1.2 cm in size and possess an average median length to median thickness of from about 1:1 to about 3:1. Bone particles generally characterized as elongate and possessing relative high median length to median thickness ratios are utilized. The elongate particles are obtained by milling or shaving the surface of an entire bone with at least 60%, preferably 90% of the bone particles being elongated. These elongated particles possess a medium length from about 2 to 200 mm and preferably from about 10 to about 100mm. These elongate bone particles can possess a median length to median thickness ratio of at least about 50:1 up to about 500:1 or more. **Preferably, at least about 60 weight percent, more preferably at least about 75 weight percent and most preferably at least about 90 weight percent of the bone particles utilized in the preparation of the bone particle-containing composition are elongate. It is noted that elongate bone particles provide an osteoimplant possessing particularly good compressive strength.** It can thus be seen that the characterization

of the Examiner that the sizes of the bone particles used in Boyce et al '187 correspond to that of the present invention is not correct. Furthermore there is no way that Boyce et al '187 could be characterized as formable. The composition fabricated in accordance with the Boyce et al '187 disclosure more preferably has a bone content ranging from about 50 to about 95 percent based on the weight of the entire composition.

As noted in the Examples of Boyce et al '187; the bone particles were mixed with different solutions such as glycerol (Examples 1, 12), cross linked with formalin (Examples 2 and 3), saline (Example 4), ethanol and ethyl cellulose (Examples 5, 6, 7, 8), and water (Examples 9, 10, 11),. There is no teaching in the examples of the carrier of the present invention, the bone particle range, the weight of the carrier and range of the same, viscosity or any concentration of cellular material (Boyce et al '187 being a solid and having no viscosity). Applicant would point out that the use of hydrogels, are disclosed only as a thickener when water and/or glycerol are used as the wetting agent for forming the slurry. These hydrogels are used to suspend and keep the bone particles separate during the application of the compression forces to form the solid structure and do not act as a carrier for the bone particles.

Chitosan is noted in Boyce et al '187 as a binder or an adhesive for the demineralized bone particles and **is incidentally found as one of a 60+ line list of suitable binders or adhesives.** (Col. 8, lns. 13-40) Preferred binders are polyhydroxybutyrate, polyhydroxyvalerate and tyrosine-based polycarbonates. When employed, binders will typically represent from about 5 to about 70 with percent of the bone particle-containing composition calculated prior to compression of the composition.

Boyce et al '187 also envisions the use of fibers which will typically represent from about

5 to about 75 weight percent of the bone particle-containing composition.

Chitosan is also noted as a thickener to be used when the wetting agent is water and/or glycerol to preclude premature bone particle separation and improve the suspension keeping characteristics of the composition (Col. 10, lns. 58-67 to Col. 11, lns. 1-10) prior to application of the compressive forces. This is used to keep the bone particles separate during application of the compressive forces to form the solid structure and not as a carrier for the bone products which is then directly applied to the wound site. Chitosan is not noted as being used in any of the Examples or in any of the preferred embodiments.

The Boyce et al '187 composition is heated in a mold during or after the compression step at a suitable temperature ranging from about 30° to about 70° C from 1 to 72 hours preferably 24 to 48 hours. Optionally it can be cross linked to improve the mechanical strength of the osteoimplant. Thus it is apparent that prior to final manufacturing steps of molding, heating and cutting the osteoimplant is not usable for application of a surgeon in the operating room.

The Boyce et al '187reference cannot be combined with Sander '629 and/or Breitbart et al. '289 and does not teach or suggest the composition of the present invention in connection with the teachings of the Sander '629 patent and/or Breitbart et al. 289.

The Sander et al. '629 reference (noted as secondary art) **discloses the making of a bone cement to fill defects in bone.** The Examiner has argued that the '629 reference teaches: (1) a composition for bone repair comprising particles dispensed in a matrix; (2) that the composition can be implanted into defective bone tissue; (3) discloses the use of drugs and other substances that can induce bone growth; (4) that biocompatible particles of any size can be used in the composition and (5) that matrix material can be conveniently comminuted to appropriate particle size.

The bone cement of Sander et al '629 is formed by mixing biocompatible particles preferably polymethylmethacrylate coated with polyhydroxyethylmethacrylate (Examples 1 , 2 and 5 - 10) or particles of glycolide-lactide copolymer (Examples 3 and 4) in a matrix to obtain a molded semi-solid mass which can be suitably worked for implantation into bone. The biocompatible particles which are dispersed in the matrix can be formed from either bioabsorbable or nonbioabsorbable material. Suitable nonbioabsorbable material which can be used to form the biocompatible particles can be derived from xenograft bone, homologous bone, autogenous bone, hydroxyapatite and polymethylmethacrylate coated with polyhydroxyethylmethacrylate, the preferred nonbioabsorbable material.. The weight of the nonbioabsorbable material in the wetted composition of Sander et al '629 runs from 35% to 75% (Dry weight 64% to 94%); to most preferably 45% to 60% (Dry weight 73% to 92%) with the more preferred weight being 40% to 70% (Dry weight 82% to 90%)(Col 4 lns 21 - 30). **There is no disclosure of demineralized bone used as the nonbioabsorbable material in Sander et al '629 and demineralized bone is used as an additive in the nature of an osteogenic agent**. This bioactive substance is included as one or more medico-surgically useful substances such as a therapeutic agent, a growth promoting factor and osteogenic agent. It is noted in Col. 4 ln 40 to Col. 5 ln 17 that a bioactive substance can be introduced into the compositions, either directly into the matrix prior to or after wetting or into the biocompatible particles or polymethylmethacrylate particles, the preferred substance being polymethylmethacrylate. A growth promoting factor can be introduced into the composition such as fibroblast growth factor, bone growth factor, epidermal growth factor, platelet derived growth factor, macrophage derived growth factor, alveolar derived growth factor, monocyte derived growth factor, magainin and so forth. The bioactive substance can also be an osteogenic agent such as

osteoinductive protein, demineralized bone powder, in addition to morselized cancellous bone, aspirated bone marrow and other autogenous bone sources. As previously noted demineralized bone powder **is an additive of undetermined amount** and is included in a general laundry list and is not taught to be the biocompatible material, but rather an osteogenic agent.

In Examples 1 and 2 of the '629 patent, polymethylmethacrylate particles were coated with polyhydroxyethylmethacrylate carboxymethylcellulose or methylcellulose and water' Examples 3 and 4 use particles of glycolide-lactide copolymer; Examples 5 and 6 use particles of polymethylmethacrylate coated with polyhydroxyethylmethacrylate hydroxypropylmethylcellulose water; and Examples 7-10, use particles of polymethylmethacrylate coated with polyhydroxethylmethacrylate. The preferred nonbioabsorbable material was mixed with a matrix **HA (hyaluronic acid) having a molecular weight of about six hundred thousand Daltons**. Indeed **in all of the Examples no bone material of any type is used**. The use of demineralized bone in the range noted present invention results in an osteoinductive material which promotes bone growth.

Sander et al. '629 has a matrix (cellulose ether, collagen, hyaluronic acid, pharmaceutically accepted salt of hyaluronic acid, derivative of hyaluronic acid and pharmaceutically acceptable salt of hyaluronic acid derivative and mixtures thereof)ranging from 6% to 36% by weight with 64% to 94% by weight of polymethylmethacrylate crystals. If one were to substitute demineralized bone material for the polymethylmethacrylate coated with polyhydroxyethacrylate of Sander et al '629, which substitution is not taught or suggested by this reference and is a completely different material, the range would be outside of the inventive range claimed.

Sander et al. '629 does not teach or obviate the present invention alone or combined with the

other cited references. Sander et al. '629 does not use or teach (1) demineralized bone material as the nonbioabsorbable material and as a major component of the composition; (2) an equivalent biocompatible material weight, (3) a carrier of chitosan; (4) a molecular weight of the carrier which is the same as the molecular weight of the inventive carrier; (5) a phosphate buffer to neutralize the composition, and (6) the addition of cellular material at a concentration of 10^5 to 10^8 per cc of the carrier. Furthermore Sander et al is not osteogenic relying on antigenic response.

The '629 reference does not suggest using demineralized bone together in a buffered isotonic salt carrier with a neutral osmolality or that such a combination is osteoinductive and medically beneficial in the repair of bone tissue. The Examiner's inference that the '629 patent teaches that the composition can comprise living cells such as erythrocytes, leucocytes and endothelial cells and that the pH of the composition is approximately 6.8-7.4 is not based on the teachings of the '629 patent and is a hind site supposition.

The Breithart et al '289 patent (noted as secondary art) is directed toward a sponge like matrix preferably constructed of a biodegradable, biocompatible synthetic polymer which uses the patient as the source of cells for the repair of bone defects. The cells are taken from the periosteum, (consisting of mainly multipotent mesodermal cells), isolated and seeded onto and into a matrix. In other embodiments, the matrix is formed of a material such as hydroxyapatite or mixtures of hydroxyapatite and polymer, or tricalcium phosphate. The matrix can also be sterilized bone or a porous metal alloy. The Examiner notes that Breithart et al '289 teaches (1) the use of chitosan: In regard to the disclosure of chitosan, in col. 6, lns. 20-40 a large laundry list (over 30 polymers) of potential natural and synthetic polymers are noted which can be used to form the fibrous matrix. Examples of natural polymers includes polysaccharides. (Col. 6 ln 38) It is quite apparent that the

matrix is solid as it is preferably made of hydroxyapatite, tricalcium phosphate, sterilized bone or metal alloy. In col. 11, lns. 27-40, chitosan is only noted for being a natural polycation such as the polysaccharide, chitosan. (Chitosan is not used as a carrier but as a cation) This is but one of a number of varieties of polycations which complex and stabilize the polymer hydrogel into a semipermeable surface membrane. Various examples are noted and it is off handedly noted, that there exists natural polycations such as the polysaccharide chitosan.

The patent to Breitbart et al. '289 is directed toward periosteum cells seeded into a matrix (preferably a synthetic polymer) for repair of the bone defect. The '289 patent does disclose stem cells, chondrocytes and mesenchyma cells as follows: Col. 2, lns. 45-60, it notes that prior art shows the use of autologous cells and chondrocytes attaching to hydroxyapatite. Col. 4, lns. 25-30 discloses the use of periosteum which consists of multipotent mesodermal cells. Col. 14, ln. 60 Claim 9 refers to periosteum cells seeded in biocompatible matrix.

Furthermore, none of the cited references disclose the additives of cells at a concentration of 10^5 - 10^8 per cc of carrier or a specific amount of growth factor added to 10cc of carrier.

In cases which are similar to the present circumstances, the courts have ruled that beyond looking at the prior art to determine if it suggests doing what the inventor has done, one must consider if the prior art provides an expectation of succeeding in the endeavor. *In re Dow Chem.,* 837 F.2d 469, 473, 5 U.S.P.Q.2d 1529, 1531 (Fed. Cir. 1988), "Both the suggestion and the expectation of success must be founded in the prior art, not in the applicant's disclosure." Id. As noted by the court in the case of *In re Clinton,* "Obviousness does not require absolute predictability, but a reasonable expectation of success is necessary." *In re Clinton,* 527 F.2d 1226, 1228, 188 U.S.P.Q. 365, 367 (C.C.P.A.1976).

As noted by the Court in the case of *In re Gordon,* the mere fact that a prior art reference could be modified to achieve the claimed invention does not make the modification obvious unless the prior art suggested the desirability of the modification. *In re Gordon,* 733 F.2d 900, 902, 221 U.S.P.Q. 1125, 1127 (Fed. Cir.1984); see also *In re Laskowski,* 871 F.2d 115, 117, 10 U.S.P.Q.2d 1397, 1398 (Fed. Cir. 1989), and *Ex parte Levengood,* 28 U.S.P.Q.2d 1300, 1302 (Bd. Pat. App. & Int. 1993). Applicants respectfully submit that nowhere in the art of record is there any suggestion to arrive at the claimed novel composition of the present invention.

The court in *Minnesota Mining & Manufacturing Co. v. Johnson &Johnson Orthopaedics, Inc.,* 24 USPQ2d 1321 (Fed. Cir 1992) held that: "Although [a patent's] specific claims are subsumed in [a prior art reference's] generalized disclosure..., this is not literal identity." The *Minnesota* court held that the reference's ranges were so broad as to be meaningless, and provided no guidance on how to construct a product with the patented invention's benefits.

The court in *In re Baird,* 29 USPQ2d 1550 (Fed. Cir. 1994), held that "The fact that a claimed compound may be encompassed by a disclosed generic formula does not by itself render that compound obvious." The *Baird* court further held that a disclosure to numerous compounds does not render obvious a claim to three compounds, particularly when that disclosure indicates a preference leading away from the claimed compounds.

As previously argued, none of the cited references singularly or in combination teach or obviate the present invention and indeed cannot be combined. The Examiner has engaged in hindsight application, a prohibited rejection since *John Deere* to combine the cited prior art references against the present invention.

C. Applicant traverses the Examiner's rejection of dependent Claims 2 and 26 as

unpatentable under 35 USC 103(a) over the cited prior art references to Boyce et al. U.S. Patent Number 6,294,187 in view of the combination of Sander et al. 5,356,629 and Breitbart et al. U.S. Patent Number 5,700,289.

The Boyce et al '187compressed bone structure is formed by applying compressive force of at least about 1000 psi, has a bulk density greater than about 0.7 g/cm^3 and a wet composite strength substantially exceeding 3MPa to form a hardened mass. The bone particles which are used in the hardened structure are formed by milling whole bone to produce fibers, chipping whole bone, cutting whole bone, fracturing whole bone in liquid nitrogen or otherwise disintegrating the bone tissue. The bone particles range in average particle size from about 0.05 to about 1.2 cm in size and possess an average median length to median thickness of from about 1:1 to about 3:1. Bone particles are generally characterized as elongate and possessing relative high median length to median thickness ratios. The elongate particles are obtained by milling or shaving the surface of an entire bone with at least 60%, preferably 90% of the bone particles being elongated. These elongated particles possess a medium length from about 2 to 200 mm and preferably from about 10 to about 100mm. These elongate bone particles can possess a median length to median thickness ratio of at least about 50:1 up to about 500:1 or more. **Preferably, at least about 60 weight percent, more preferably at least about 75 weight percent and most preferably at least about 90 weight percent of the bone particles utilized in the preparation of the bone particle-containing composition are elongate. It is noted that elongate bone particles provide an osteoimplant possessing particularly good compressive strength.** It can thus be seen that the characterization of the Examiner that the sizes of the bone particles used in Boyce et al '187 correspond to that of the present invention is not correct. Furthermore there is no way that Boyce et al '187 could be

characterized as formable. The composition fabricated in accordance with the Boyce et al '187 disclosure more preferably has a bone content ranging from about 50 to about 95 percent based on the weight of the entire composition. Neither Sander et al '629 nor Breithart et al '289 teach allograft cortical bone sized at 100 - 850 microns in the weight concentration set forth in these two dependent claim.

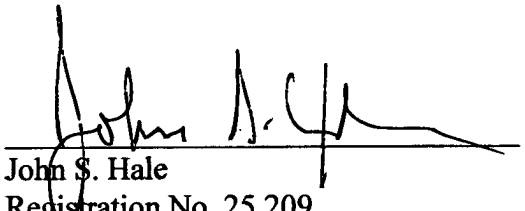
SUMMARY OF ARGUMENT

The respective grounds of final rejection of the claims of this application under 35 USC 103(a) are incorrect for the reasons advanced above. Reversal thereof by the Honorable Board of Patent Appeals and Interferences is therefore requested and is earnestly solicited.

Our check in the amount of $500.00 is attached to cover the cost of filing this Brief and two copies. Oral hearing will be requested during the rebuttal time period. If any additional fees are incurred, kindly charge the same to our Deposit Account No. 07-1340.

Respectfully submitted,

GIPPLE & HALE



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CLAIMS APPENDIX

1. (Canceled)

2. A sterile formable bone composition as claimed in claim 21 wherein said bone particles are allograft cortical bone ranging from 100 microns to 850 microns in size at a concentration ranging from 20% to 35% by weight of the composition.

3. (Canceled)

4. (Canceled)

5. (Canceled)

6. (Canceled)

7. A sterile formable bone composition as claimed in claim 21 wherein said bone particles are taken from a group consisting of allograft bone, cortical allograft bone, corticalcancellous bone, cancellous bone, autologous bone and xenograft bone

8. A sterile formable bone composition as claimed in claim 21 wherein said composition includes bone chips taken from a group consisting of partially demineralized chips and non demineralized chips having a particle size ranging from 0.1mm to 1.0cm which are added to said viscous carrier at a concentration of about 5% to about 25%.

9. (Canceled)

10. (Canceled)

11. (Canceled)

12. (Canceled)

13. (Canceled)

14. (Canceled)

15. (Canceled)

16. (Canceled)

17. (Canceled)

18. (Canceled)

19. (Canceled)

20. (Canceled)

21. A sterile formable bone composition for application to a bone defect site to promote new bone growth at the site comprising a demineralized osteoinductive and osteoconductive bone particles in an aqueous carrier solution, the bone particles being added to a viscous carrier at a concentration ranging from 5-50%(w/w), the carrier comprising a hydrogel taken from a group consisting of chitosan and sodium alginate in a phosphate buffered aqueous solution, said hydrogel ranging from about 5.0% to about 20.0% by weight of the aqueous carrier solution and said hydrogel component having a molecular weight ranging from ten thousand to three hundred thousand Daltons with a stable viscosity at a temperature ranging from about 22° C to about 37°C and said composition having a pH ranging from about 6.8 to about 7.4 and a growth factor additive added to said composition, said growth factor comprising one or more of a group consisting of transforming growth factor (TGF-beta), insulin growth factor (IGF-1); platlet derived growth factor (PDGF), vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF) (numbers 1-23), osteopontin, growth hormones such as somatotropin cellular attractants and attachment agents.

22. A sterile formable bone composition as claimed in claim 21 including a cellular material additive taken from a group consisting of living cells and cell elements such as chondrocytes, red blood cells, white blood cells, platelets, blood plasma, bone marrow cells,

mesenchymal stem cells, pluripotential cells, osteoblasts, osteoclasts, and fibroblasts, epithelial cells, and endothelial cells, said cells or cell elements or combinations of the same being present at a concentration of 10^5 to 10^8 per cc of the carrier.

23. A sterile formable bone composition for application to a bone defect site to promote new bone growth at the site comprising demineralized osteoinductive and osteoconductive allograft bone particles in an aqueous carrier solution, the bone particles being added to a viscous carrier at a concentration ranging from 5-50%(w/w), the carrier comprising a chitosan in a phosphate buffered aqueous solution, said hydrogel chitosan ranging from about 5.0% to about 20.0% by weight of the aqueous carrier solution and cellular material taken from a group consisting of living cells, cell elements such as red blood cells, white blood cells, platelets, blood plasma, pluripotential cells, osteoblasts, osteoclasts, and fibroblasts, epithelial cells, and endothelial cells present at a concentration of 10^5 to 10^8 per cc of the carrier, said hydrogel component having a molecular weight ranging from ten thousand to three hundred thousand Daltons with a stable viscosity and said composition having a pH ranging from about 6.8 to about 7.4

24. A sterile formable bone composition as claimed in claim 23 including growth factor additive added to said composition, said growth factor comprising one or more of a group consisting of transforming growth factor (TGF-beta), insulin growth factor (IGF-1); platlet derived growth factor (PDGF), vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF) (numbers 1-23), osteopontin, growth hormones such as somatotropin cellular attractants and attachment agents.

25. A sterile formable bone composition as claimed in claim 23 including growth factor additive added to said composition comprising one or more of a group consisting of fibroblast

growth factor (FGF) (numbers 1-23) in the amount of 2-4 milligrams in 10cc of carrier solution.

26. A sterile formable bone composition as claimed in claim 23 wherein said bone particles are allograft cortical bone ranging from 100 microns to 850 microns in size at a concentration ranging from 20% to 35% by weight of the composition.

27. A sterile formable bone composition as claimed in claim 23 wherein said bone particles are taken from a group consisting of allograft bone, cortical allograft bone, corticalcancellous allograft bone and cancellous allograft bone, autologous bone and xenograft bone.

28. A sterile formable bone composition as claimed in claim 23 wherein said composition includes bone chips taken from a group consisting of partially demineralized chips and non demineralized chips having a particle size ranging from 0.1mm to 1.0cm which are added to said viscous carrier at a concentration of about 5% to about 25%.